Amendment

Protocol Number: 11C0149-D **Reference Number:** 370610

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Protocol Title: Evaluation of Diagnostic and Prognostic Molecular Markers in Adrenal Neoplasm

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CONCURRENCE

OPS Protocol Specialist:

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Signature	Print Name	Date

* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

Abbreviated Title: Adrenal Neoplasm

CC Protocol: 11-C-0149 D

Version Date: 06/05/2017

NCT Number: NCT01348698

Title: Evaluation of Diagnostic and Prognostic Molecular Markers in Adrenal Neoplasm

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Investigators Roles	A. Obtain information by intervening or interacting with living individuals for research purposes B. Obtaining identifiable private information about living individuals C. Obtaining the voluntary informed consent of individuals to be subjects D. Makes decisions about subject eligibility E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes G. Some/all research activities performed outside NIH

PRÉCIS

Background:

- Adrenal neoplasms are common and are incidentally discovered in 4-10% of abdominal imaging studies.
- The majority of adrenal incidentalomas are cortical adenoma.
- Many patients with nonfunctioning adrenal incidentalomas undergo adrenalectomy to exclude a cancer diagnosis.
- There are no reliable clinical, radiographic or laboratory studies that accurately distinguish between localized benign and malignant adrenal neoplasm.
- This protocol is designed to determine the feasibility and accuracy of using novel molecular markers of malignant adrenal neoplasm in fine needle aspiration (FNA) biopsy and surgically resected samples.

Objectives:

- Primary Objectives:
  - To evaluate the feasibility of molecular testing in adrenal neoplasm FNA biopsy samples.
  - To determine the accuracy of novel diagnostic molecular markers in clinical adrenal FNA biopsy and surgically resected samples.
- Secondary Objectives
  - To analyze the gene expression level relative to disease-free survival and overall survival in patients with adrenocortical carcinoma

Eligibility:

- An individual with an adrenal neoplasm greater than 2 cm in size
- Age $\geq$ 18 years
- Adults must be able to understand and sign the informed consent document

Design:

- Prospective observational study.
- Demographic, clinical, laboratory and pathologic data will be collected for each patient participant. Data will be securely stored in a computerized database.
- Patients will have biochemical testing to determine if their adrenal neoplasm is functioning or nonfunctioning.
- After their initial on-study evaluation, patients who are found to have a nonfunctioning adrenal tumor with a low risk of malignancy will be re-screened every year for 5 years with non-invasive imaging studies.

- Treatment of patients with an adrenal neoplasm will be performed based on standard clinical practice.
- Projected accrual will be 50 patients per year for a total of 10 years. Thus, we anticipate accruing 500 patients on this protocol.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives:

- To evaluate the feasibility of molecular testing in adrenal neoplasm FNA biopsy samples.
- To determine the accuracy of novel diagnostic molecular markers in clinical adrenal FNA biopsy and surgically resected samples.

1.1.2 Secondary Objectives

- To analyze the gene expression level relative to disease-free survival and overall survival in patients with adrenocortical carcinoma

1.2 BACKGROUND AND RATIONALE

Adrenal neoplasms are one of the most prevalent of all human tumors [1]. The prevalence of adrenal incidentaloma is approximately 5% on abdominal imaging, but the prevalence can be as high as 10% in the elderly. As the U.S. population ages, the management of adrenal incidentaloma will be an increasingly important issue in health care [1]. As outlined in a NIH State-of-the-Science statement on the "Management of the Clinically Inapparent Adrenal Mass (Incidentaloma)" there are significant limitations in diagnostic evaluation of these tumors because there are no reliable criteria for predicting the risk of malignancy, outside of obvious metastatic or locoregional disease [2]. This results in many patients having adrenalectomy to exclude a cancer diagnosis [3, 4]. For this reason, we will test the feasibility and determine the accuracy of novel diagnostic molecular markers in adrenal neoplasm FNA biopsy and in surgical resected samples.

There are no reliable preoperative clinical, imaging or biochemical tests available to distinguish between primary benign and malignant adrenocortical neoplasms in the absence of obvious metastatic disease or locoregional invasion [5]. Imaging features such as tumor heterogeneity, irregular tumor border, hemorrhage, necrosis, rapid tumor growth rate, tumor Hounsfield unit >10-20 on non-contrast CT scan, and intravenous contrast washout of 40% or less after 15 minutes are more common in malignant tumors but are not reliable enough to avoid the need for adrenalectomy to exclude a cancer diagnosis nor to forgo continued follow up [5-10]. In patients with a history of an extra-adrenal malignancy, an adrenal incidentaloma may indicate metastatic disease in 32% to 73% of cases depending on the primary tumor site and patient age [1, 11]. The tumor size of adrenal neoplasm measured by imaging studies has been used as a preoperative surrogate marker for a malignant tumor and for recommending resection, but this criterion is not precise for tumors that measure > 2 cm but < 6 cm [2, 12]. Even when the tumor is 6 cm or larger, the reported risk of malignancy ranges from 5% to 98%, depending on the study cohort [5, 13, 14]. In many centers, a size threshold of > 6 cm has been used as an absolute indication for adrenalectomy. However, it is unclear whether adrenal tumors between 2 cm and 6 cm should be removed or monitored, whereas most experts recommend monitoring tumors < 4 cm in size depending on the patient's age.

Fine needle aspiration biopsy and cytologic examination has not been routinely used to evaluate adrenal neoplasm at most centers because it is not accurate enough for

distinguishing between primary benign and malignant adrenocortical tumors [15-19]. However, in patients with a concurrent malignancy or history of extra-adrenal malignancy, fine needle aspiration biopsy may be useful for detecting metastatic disease to the adrenal gland after biochemical exclusion of a hyperfunctioning tumor, especially a pheochromocytoma [15-19]. Fine needle aspiration of the adrenal gland is associated with a low risk (<1%) of complications such as bleeding, pneumothorax, pain, and rarely tumor seeding along the needle track [1, 20].

Postoperative histopathologic examination to distinguish between malignant and benign primary adrenal tumors is also difficult and problematic. For adrenocortical neoplasms, the Weiss histologic criterion is most commonly used, but is imprecise [21-23]. This means even patients with histologically diagnosed adrenocortical adenoma require continued follow-up because some will develop metastatic disease [11].

In summary, although adrenocortical carcinomas tend to be larger than benign tumors, tumor size, even when combined with imaging features, is not accurate enough to use for making management decisions for most tumors that are less than 6 cm. Furthermore, imaging studies such as MRI and CT scans underestimate adrenal tumor size by 16% to 47%, and are less accurate in smaller tumors [24-26]. Therefore, there is a significant need for biomarkers that can distinguish benign from malignant adrenal tumors for determining the need for adrenalectomy, for selecting the appropriate surgical approach, and for determining the appropriate follow up.

We and others have used genome profiling approaches (mRNA, microRNA) to identify diagnostic and prognostic markers of malignant adrenocortical tumors [27-31]. In our studies, we have identified several novel diagnostic markers with excellent accuracy for distinguishing between benign and primary malignant adrenocortical tumors (**Appendix A**). While these markers could be used in post-surgical resection samples in equivocal cases, the most helpful clinical application of these markers would be preoperatively in clinical fine needle aspiration biopsy samples. Therefore, we propose to test the feasibility and accuracy of using this panel of markers in fine needle aspiration samples of patients with adrenal neoplasm with the exception of pheochromocytoma that are greater than 2 cm. For cytologic examination, fine needle aspiration biopsy has a 67%-100% adequacy rate [32, 33]. Our previous studies in thyroid fine needle aspiration biopsy samples indicate an adequate yield of nucleic acid for multigene expression analysis [34]. Moreover, we are able to determine gene expression levels in as little as 10 adrenocortical carcinoma cells by quantitative RT PCR (**Appendix B**).

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 INCLUSION CRITERIA

a. An individual with a primary localized adrenal neoplasm greater than 2 cm in size

b. Age $\geq$ 18 years

c. Adults must be able to understand and sign the informed consent document

d. Patients must have an ECOG performance score of 0-2.

e. Patients must have laboratory and physical examination parameters within acceptable limits by standard of practice guidelines prior to biopsy or surgery

Note: patients with suspected but unconfirmed adrenal neoplasm may be enrolled.

2.2 EXCLUSION CRITERIA

a. Biochemically proven Pheochromocytoma

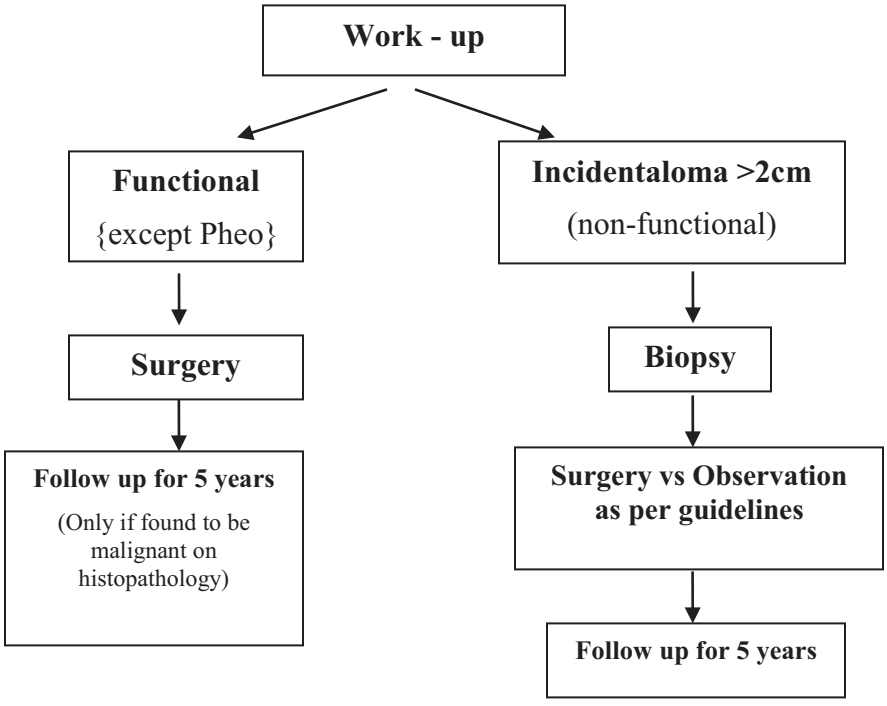
b. Women who are pregnant because of the possible side effects of radiation from CT-guided biopsies to the unborn child.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

3 STUDY IMPLEMENTATION

This is a prospective study of individuals with an adrenal mass. Individuals will have routine clinical work up for an adrenal mass (see section **3.1**); those with nonfunctioning tumors larger than 2 cm will undergo CT guided fine-needle aspiration biopsy. For patients who require adrenalectomy for a functioning tumor, the surgically resected tissue sample will be used for the molecular analysis.



3.1 On Study Evaluation

Patients will undergo the following evaluations which may be performed within 4 weeks of enrollment:

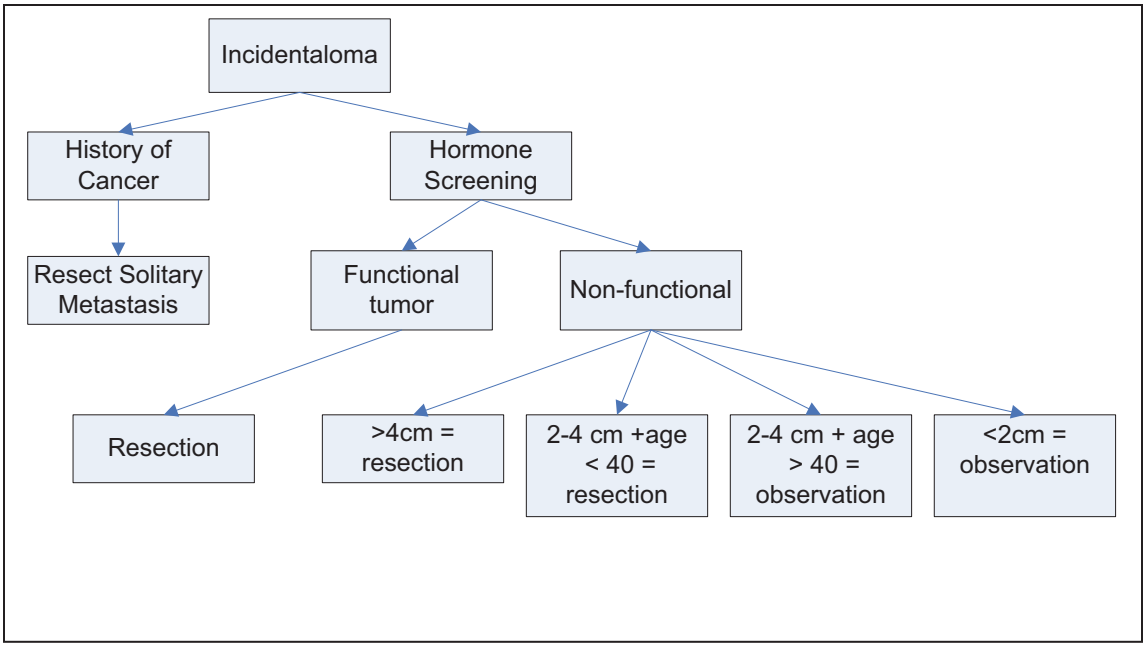
- Detailed History and Physical Examination including, vital signs, ECOG status, demographic information and family history.
- Imaging studies
- Adrenal protocol CT scan with and without intravenous contrast.
- FDG PET/CT scan
- Laboratory evaluations
  - CBC with differential
  - Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, Total CK, Uric Acid
  - PT/PTT
- Biochemical testing
  - Serum renin and plasma aldosterone levels
  - 24-hour urinary cortisol level
  - Low dose (1-2mg) dexamethasone suppression test
  - Serum fractionated plasma normetanephrine and metanephrine

3.2 CT guided fine needle aspiration biopsy of adrenal neoplasm

- Patients with confirmed non-functional tumors greater than 2 cm in greatest dimension will undergo CT guided fine needle aspiration in the Interventional Radiology Department as per standard of care if they do not require an adrenalectomy.
- Tissue will be handled as described in Section **5.1.1**

3.3 Surgical Intervention

Patients with an adrenal neoplasm will have an adrenalectomy based on our standard clinical practice (**Appendix C***).



*Patients with an adrenal mass measuring 2 – 4cm and suspicious imaging features for malignancy will be given the option of adrenalectomy.

3.4 FOLLOW-UP EXAMINATIONS

3.4.1 Patients who are found to have an adrenal neoplasm which does not require resection will undergo the following evaluations every year for 5 years:

- Physical exam to include vital signs and ECOG status
- Laboratory evaluations - all tumors
  - 24-hour urinary cortisol level
  - Low dose (1-2mg) dexamethasone suppression test
  - Serum fractionated plasma normetanephrine and metanephrine
  - Serum renin and plasma aldosterone levels
- Adrenal protocol CT scan with and without intravenous contrast.

3.4.2 Patients who undergo an adrenalectomy will undergo the following evaluations every year for 5 years (only if found to be malignant on histopathology):

- Physical exam to include vital signs and ECOG status
- Laboratory Evaluations
  - 24-hour urinary cortisol level
  - Low dose (1mg) dexamethasone suppression test (only for those patients with non-functioning tumors)
- CT scan of the chest, abdomen and pelvis to exclude disease recurrence

Note: Patients who are unwilling or unable to travel to the NIH Clinical Center for follow up may have the examinations performed at home with the results sent to the research team.

Note: Patients may be evaluated on a more frequent basis if they develop symptoms possibly associated with their adrenal neoplasm. Patients who meet the criteria for adrenalectomy at any time during the follow up period will be offered surgical intervention at the NIH Clinical Center. Patients who require chemotherapy will be offered a clinical trial at the NIH Clinical Center if they are eligible, or will be referred to their home oncologist for care.

3.5 OFF STUDY CRITERIA

Patients will be removed from the study if any of the following criteria are met:

- the patient requests withdrawal from the study
- the patient is consistently non-compliant with follow-up appointments
- the patient is consistently non-compliant with imaging studies.
- Completion of the protocol specified follow up period
- Loss of capacity to provide informed consent
- PI decision to close the study

3.5.1 Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

Supportive care will be provided to the patients as is indicated by their endocrine neoplasm and procedures performed. The clinical evaluations done as part of this protocol may detect an unsuspected malignancy or other serious medical conditions. When this occurs, referral for treatment is expedited. If a participant requires cancer treatment and meets the eligibility criteria for an active CCR protocol, we will try to facilitate the referral process, but we cannot promise study participants treatment as part of the protocol. Otherwise, referral is made to qualified therapists at regional cancer centers or in the patient's home community.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 Adrenal biopsy and surgical specimens

The adrenal fine needle aspiration will be performed at the NIH Clinical Center. Patients will undergo one biopsy. A portion of the FNA sample will be sent to the department of pathology, and the remainder to the Endocrine Oncology laboratory. The biopsy sample will be immediately placed in RNAlater®, transported on ice, and stored in -80°C until used for molecular analysis. For the surgical resection specimen, the samples will be immediately snap frozen in liquid nitrogen and stored in -80°C until molecular analysis.

Samples will be immediately transported to:

NCI Endocrine Oncology Laboratory
CRC Room 3-5840
10 Center Drive, MSC 1201
Bethesda, MD 20892-1201
(301) 435-7891

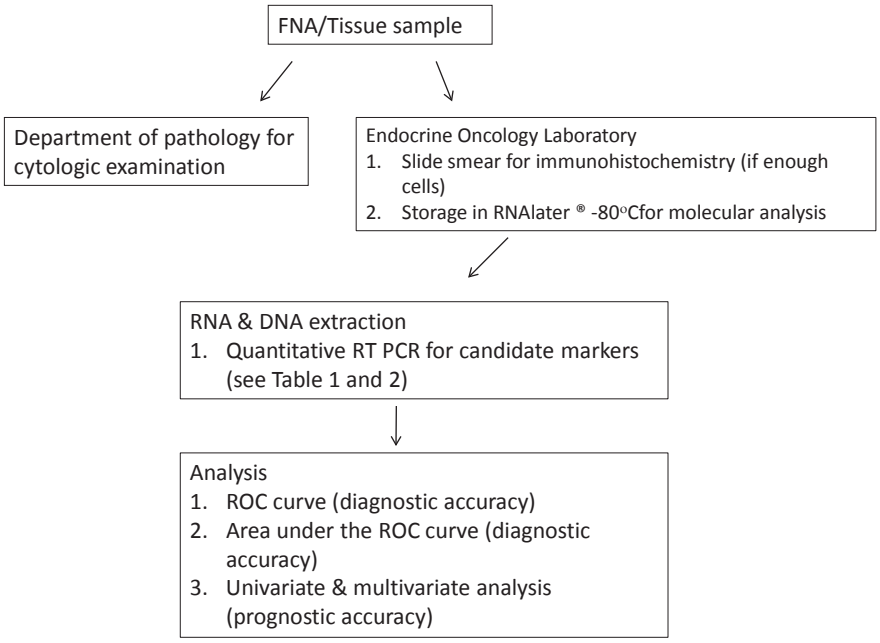


Figure 1. Flow diagram of specimen collection and analysis.

The diagnostic accuracy of the candidate gene expression levels will be determined based on the histologic diagnosis and follow up time of over 5 years. We will also analyze the gene expression level relative to disease-free survival and overall survival in patients with adrenocortical carcinoma. All the candidate gene expression level thresholds/cutoffs will be normalized to an adrenocortical carcinoma cell line and universal RNA to account for interassay variability.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

- Specimens will be collected and analyzed as noted above.
- Samples will be labeled with the date and time of acquisition, the type of tissue and patient study number in the Labmatrix database.
- Tissue will be stored in the NCI Endocrine Oncology lab.
- At the completion of the protocol, the investigator will dispose of all specimens in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland. Any loss or unintentional destruction of the samples will be reported to the IRB.
- No samples will be stored for ongoing and future research on this protocol.
- Patients who are willing to have samples stored for future and ongoing research will be enrolled on 09-C-0242 *Prospective Comprehensive* Molecular *Analysis of Endocrine Neoplasms*.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data prior to and during the course of the patient's participation will be collected in order to monitor patient eligibility, and will include review of medical and family history records, non-invasive imaging, blood work, and urinary studies. Data will be securely stored in the Labmatrix database.

All details of patient evaluation, management and treatment will be documented in the patient medical record. Only the following information will be captured on the CRFs:

- Detailed demographic information including family history
- Laboratory results
- Imaging results (CT scan)

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

I will share de-identified human data generated in this research for future research

- in a NIH-funded or approved public repository clinicaltrials.gov
- in BTRIS
- in publication and/or public presentations
- at the time of publication or shortly thereafter.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

All patients will undergo monitoring of their disease, operative intervention when indicated, and follow up as per standard of care. Patients who meet the standard of care criteria for resection of their disease will undergo a major operative procedure and may receive extensive care in the ICU. The principal investigator or designee will closely monitor and document the clinical care and treatment of each patient as per standard of care at the NIH Clinical Center. As per NIH Clinical Center standards of practice, the Occurrence Reporting System will be used to report any clinical events meeting these reporting criteria.

Patients who meet specific criteria described in Section **3.2** will undergo an adrenal biopsy. Adverse events will be collected in this cohort only from the time of the biopsy through 30 days post biopsy or until the date of surgery, whichever comes first. (No adverse events will be collected or reported on this protocol for patients undergoing standard of care procedures.)

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether

or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the intervention and have an attribution of at least possibly related to the intervention should be recorded and reported.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the research procedure caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the research procedure and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a research procedure.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.8 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
- (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
- (b) the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 unexpected events that are possibly, probably or definitely related to the research that occur within 30 days of biopsy (or until day of surgery, whichever comes first)
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research that occur within 30 days of biopsy (or until day of surgery, whichever comes first)
- All Grade 5 events regardless of attribution that occur within 30 days of biopsy (or until day of surgery, whichever comes first)
- All Serious Events regardless of attribution and occur within 30 days of biopsy (or until day of surgery, whichever comes first)

NOTE: Grade 1 events are not required to be reported.

7.3 DATA AND SAFETY MONITORING PLAN

7.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively enrolled on the trial to discuss each patient.
Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB via iRIS.
The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine the ability of a set of markers to distinguish between benign and malignant adrenocortical neoplasms.
Patients with adrenal neoplasms greater than 2 cm will be enrolled onto the trial and a set of novel diagnostic and prognostic molecular markers will be evaluated. It is anticipated that approximately 10% of patients enrolled will have a malignant mass and 90% will be benign. Based upon pilot data, it is expected that the classification accuracy of the proposed methods will be 90% or better, but this study is intended to determine if this is correct and to improve the precision of the estimate of these results.
Assuming that 10% of patients have a malignant mass, it would be desirable to estimate the fraction of these correctly identified as being malignant, with a confidence interval width of +/10% or less. Enrolling thirty five (35) patients who are ultimately determined to have malignant masses would permit an associated two-sided 95% confidence interval around 90% to have a width of +/-9.9%. It would also be desirable to estimate the fraction correctly identified as being benign. Enrolling 200 patients who are ultimately determined to have benign masses would permit an associated two-sided 95% confidence interval around 90% to have a width of +/-4.2%. Greater numbers of patients and a higher probability of correct classification will result in greater precision of the estimated classification probability.
Because the estimate is likely to be much less precise for identifying the malignant cases than for identifying those that are benign, it is important to enroll sufficient patients to ensure that at least 35 malignant cases are evaluated. Thus, if 10% is a reasonable estimate of the proportion of all patients expected to have malignant masses, it would be

desirable to enroll 350-500 total patients in order to have a reasonably high probability of obtaining at least 35 with malignant masses.
Classification will be done using standard logistic regression models and ROC curves as appropriate. The sensitivity and specificity will be reported along with 95% two-sided confidence intervals, and an AUC relative to the ROC curve will be determined. It is assumed that 50 patients per year may enroll onto this study. Thus, an accrual period of 10 years is anticipated in order to enroll up to 500 subjects.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

Subjects will be selected for this protocol based on a clinical diagnosis of an adrenal neoplasm. Only patients at low risk for a malignant tumor will undergo fine needle aspiration biopsy and those requiring an adrenalectomy will have surgical resected tissue to test the markers. Such a selection criteria for performing the fine needle aspiration biopsy would allow us to select those patients most likely to represent a diagnostic dilemma and to benefit from such an analysis.

9.2 PARTICIPATION OF CHILDREN

Because adrenal neoplasm are exceedingly rare in children and when present are more likely to be malignant, children will not be enrolled in this study.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Subjects who lose capacity to provide consent will be taken off study.

9.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Participants may experience no personal benefit from the study. There is however the potential benefits of increasing our ability to diagnose and predict the outcome of patients with malignant adrenocortical neoplasms. Each individual patient would have a complication risk of <1% associated with the fine needle aspiration biopsy.

9.4.1 Specimen Collection Risks

Risks also include those associated with specimen collection include pain, bleeding and the possibility of infection at the sampling site. Risk of biopsy: All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsy, immediate medical treatment is available at the NIH's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

9.4.2 Risks of exposure to ionizing radiation

This research study involves one CT guided biopsy collected for research purposes only. Subjects undergoing this biopsy collection will be exposed to 0.80 rem. This amount of radiation is below the guideline of 5 rem per year allowed for adult research subjects by the NIH Radiation Safety Committee.

9.5 CONSENT PROCESS AND DOCUMENTS

All patients who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or one of his designees will perform the consenting process. Patients will be asked to read the consent and will be encouraged to ask questions. Separate consents will be obtained for any surgical procedures performed.

9.5.1 Telephone consent

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.
The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.5.2 Informed consent of non-English speaking subjects

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10

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11 APPENDICES

11.1 APPENDIX A

Molecular markers of adrenocortical carcinoma

Table 1. Messenger RNA candidate diagnostic markers

Gene Symbol	P value* (1)	P value* (2)	AUC (1)	AUC (2)
PRLR	0.011	0.01	0.74	0.75
HSD3B2	< 0.01	0.01	0.77	0.75
PRG-3	< 0.01	0.01	0.76	0.75
LGR5	0.01	0.008	0.74	0.76
FREM2	0.006	< 0.01	0.70	0.80
ALDH1A1	< 0.01	< 0.01	0.76	0.81
CCNB2	< 0.01	< 0.01	0.86	0.84
SLC16A9	< 0.01	< 0.01	0.80	0.87
RARRES2	< 0.01	< 0.01	0.86	0.88
HTR2B	< 0.01	< 0.01	0.87	0.88
IL13RA2	< 0.01	< 0.01	0.90	0.91

Abbreviations: AUC, area under the receiver operating characteristic curve.

**P* values were determined by Mann-Whitney test.

(1) = Analysis based on benign (54 adrenocortical adenoma, 20 adrenocortical hyperplasia, 4 normal adrenocortical tissue) and malignant (11 primary adrenocortical carcinomas) tissue samples.

(2) = Subset analysis of benign vs. malignant adrenocortical tumors excluding Conn's syndrome (n= 30) and normal (n= 4) adrenocortical tissue samples.

The combination of the highest AUC 5 genes did not show improvement in diagnostic accuracy when compared to the highest individual value (AUC: 0.913 for IL13RA2 vs. 0.907 all 5 genes in combination. Comparison of the 5 markers with the highest AUC to tumor size, one of the main current clinical criterions used to assess risk of malignancy, demonstrates that the candidate markers in combination are more accurate than tumor size (**Figure 1**).

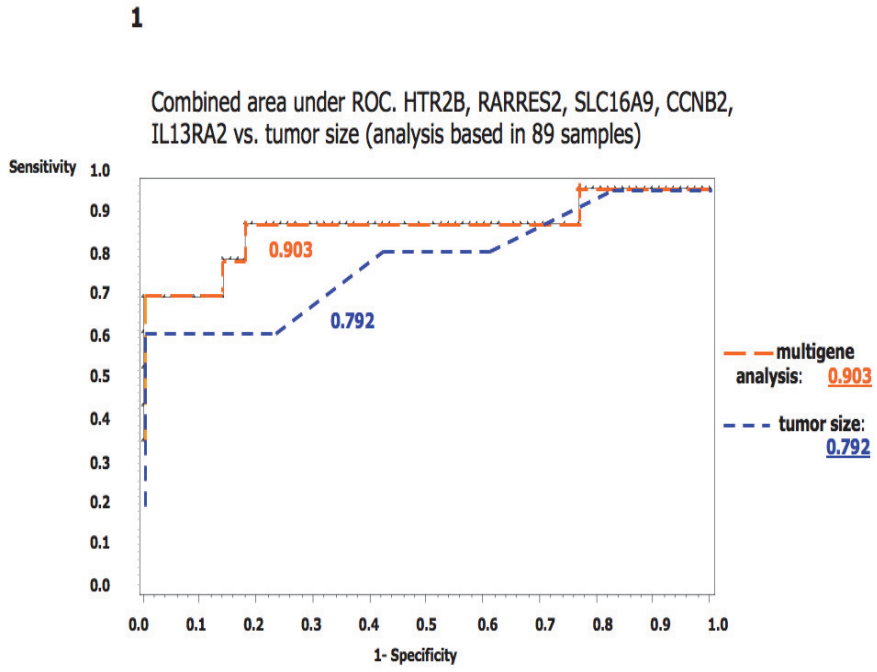


Figure 1. Area under receiver operating characteristics curve (AUC) when the 5 biomarkers with the highest individual AUC values (IL13RA2, HTR2B, CCNB2, RARRES2, SLC16A9) were combined as compared to tumor size as a clinical parameter for the diagnosis of adrenocortical carcinoma (AUC: 0.79). An AUC of 1 represents the perfect diagnostic biomarker without any false-negative and false-positive results.

Table 2. MicroRNA Candidate Diagnostic Markers

microRNA^	p value (Benign v. Malignant)	AUC
miR-665	0.0042	0.83
miR-483-5p*	<0.0001	0.94
miR-483-3p*	<0.0001	0.94
miR-23b	0.0376	0.78
miR-195*	0.014	0.77
miR-125b	0.0173	0.76

Abbreviations: AUC, area under the receiver operating characteristic curve.

P values were determined by Mann-Whitney test.

Analysis based on benign (54 adrenocortical adenoma) and malignant (11 primary adrenocortical

carcinoma) tissue samples.

*Also identified as a prognostic marker in patients with adrenocortical carcinoma

^Only microRNAs with AUC of 0.75 or higher listed and will be analyzed in this study

11.2 APPENDIX B

Analysis of gene expression levels in the NCI H295R adrenocortical cell line demonstrate that microRNA expression is detected in as little as 10 cells.

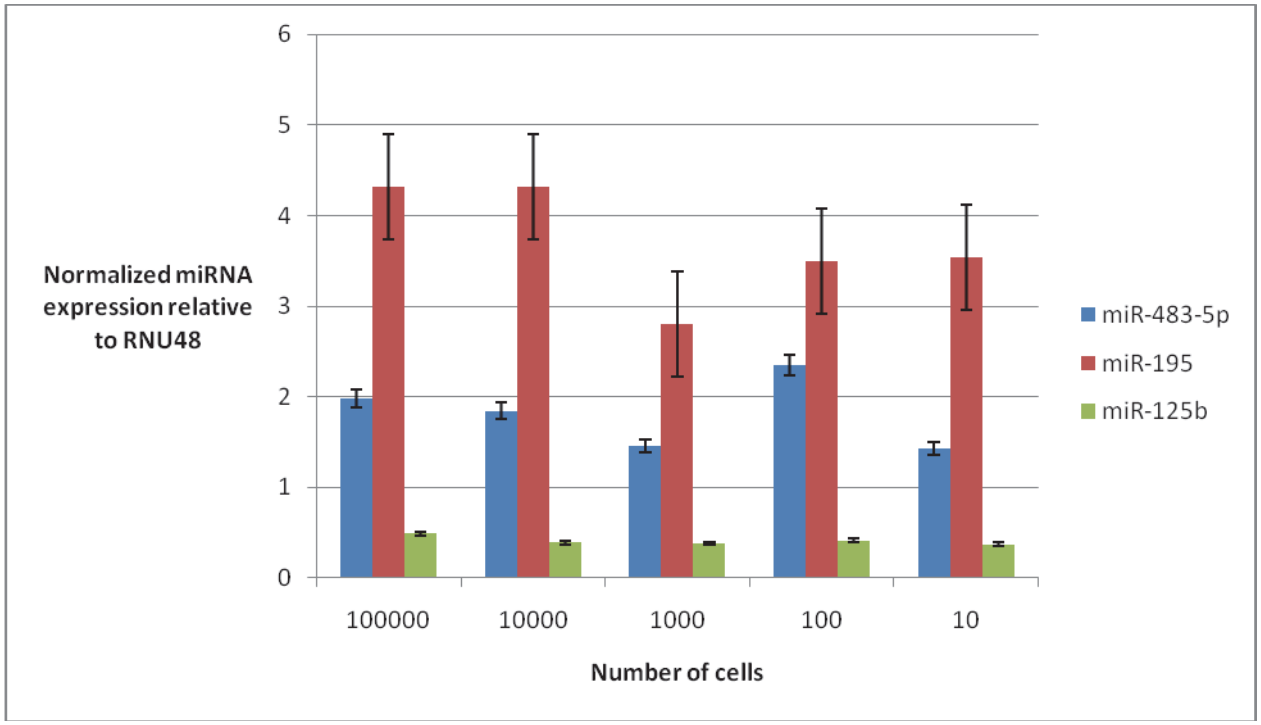
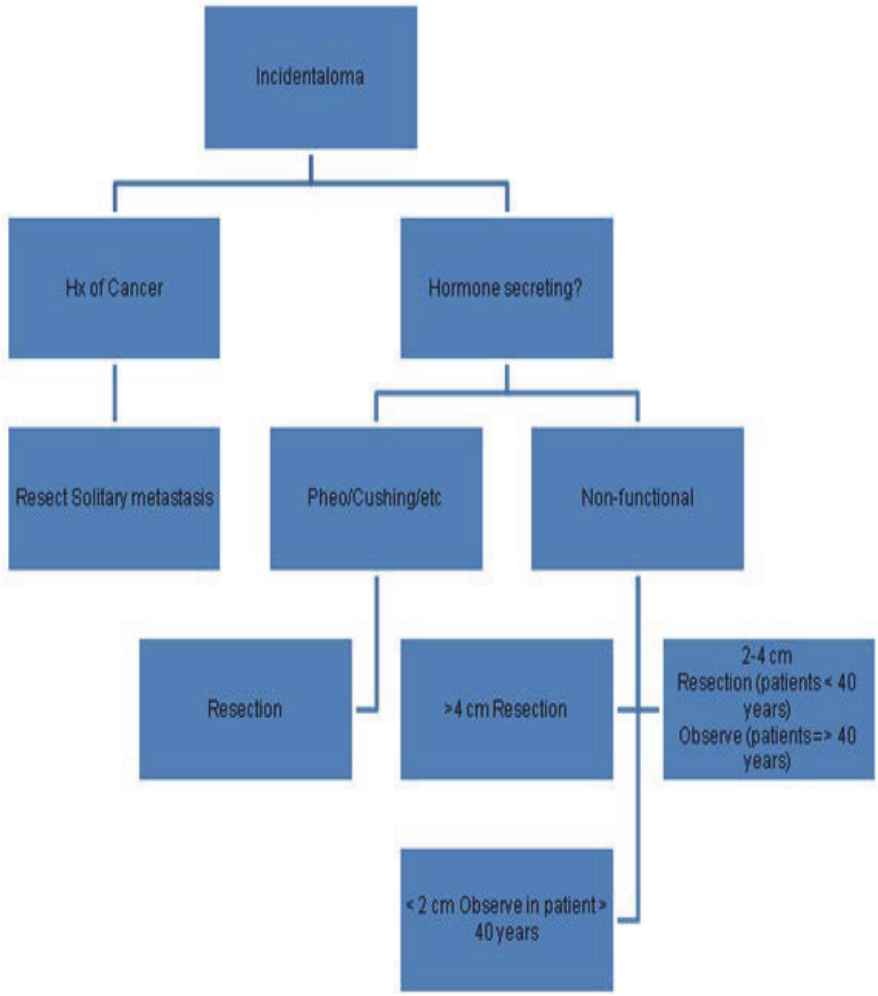


Figure 1. MicroRNA expression level by quantitative PCR.

11.3 APPENDIX C

Clinical algorithm for adrenal neoplasm work up and indication for adrenalectomy



INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0149 PRINCIPAL INVESTIGATOR: Electron Kebebew, M.D.

STUDY TITLE: Evaluation of Diagnostic and Prognostic Molecular Markers in Adrenal Neoplasm

Continuing Review Approved by the IRB on 08/08/16
Amendment Approved by the IRB on 06/28/17 (D) Date posted to web: 07/07/17

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

Adrenal tumors are common and most of them are not cancerous and cause no harm. Currently, there are no reliable tests that can accurately tell which adrenal tumors are cancerous and which are not; the only way to tell is to remove the tumor during a surgical procedure. Therefore, many patients undergo surgery who may not need to do so. In our laboratory we are analyzing tissue samples using new methods that identify specific markers and pieces of RNA that may indicate whether or not the cells are cancerous or have the potential to become cancerous. If we can accurately tell which tumors are cancerous and which are not, then we will be better able to determine which patients will benefit from surgery.

Why are you being asked to take part in this study?

You are being asked to participate in this study because you have an adrenal tumor that may or may not be cancerous.

How many people will take part in this study?

Up to 500 individuals who have a tumor in the adrenal gland will be asked to participate in this study.

Before you begin the study

Before you enroll in the study you will have lab tests, imaging studies, and a physical exam to be sure that it would be safe for you to have a biopsy or surgery and to make certain that you do not have a very specific type of adrenal tumor (pheochromocytoma).

During the study

If you are eligible for the study, you will be asked to return to the NIH Clinical Center for a biopsy and/or surgery. Prior to either, you will be asked to stop any blood thinners you may be taking.

If your tumor is not "functional" (does not secrete hormones) you will undergo one biopsy in the interventional radiology department. You will be given a local anesthetic and intravenous sedation to keep you comfortable. During the biopsy, the radiologist will insert a long thin needle into the tumor and withdraw a small piece of tissue to be sent to the Endocrine Oncology lab for testing. Following the procedure, you will return to the patient care unit to recover from the procedure – usually for about 24 hours. You will be asked to sign a separate consent for the biopsy. This biopsy is not a "standard" procedure for patients with this type of tumor and will not alter your treatment plan.

If your tumor is a "functional tumor", secretes hormones that may give you symptoms, e.g., adrenalin which may cause changes in your heart rate or blood pressure, or hormones that may cause flushing, or your tumor is large, you will undergo standard of care surgery to remove the tumor. During the surgery, a small piece of tumor will be sent to the Endocrine Oncology lab to be tested, the rest of your tumor will be sent to the Laboratory of Pathology to determine the type of tumor and whether or not there are cancer cells present. You will then recover either in the ICU or on the patient care unit until you are ready to be discharged to home. You will return to the NIH Clinical Center between 2 and 6 weeks following discharge. The length of time it will take you to recover will depend on the type of operation needed to remove your tumor. Your surgeon will explain the procedure in detail and answer any questions you may have. You will be asked to sign a separate consent for the operation.

Tissue that is sent to the endocrinology lab will be analyzed to look for markers that may indicate the cells are cancerous or may become cancerous in the future. These results are not necessary for your clinical care and will not be available until all of the samples have been analyzed.

If you have surgery or a biopsy, you will be asked to return to the NIH Clinical Center every year for about 5 years (only if cancer cells are present in your pathology results). At each visit you will have imaging studies, lab tests and a physical examination. If you do not have surgery and your

tumor grows or becomes functional, you will be offered surgery here at the Clinical Center. If you require chemotherapy, you may participate in a clinical trial here if you are eligible, or you will be referred to your home oncologist for additional treatment. Your physician may ask you to be seen more frequently if he thinks it is in your best interest. You will not be given the results of the testing performed in the endocrine Oncology lab as we may not know whether or not the information is useful until all of the patients have completed the follow up period.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because it is best to avoid radiation exposure to unborn children since they are more sensitive to radiation than adults. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control, If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Biopsy

A small amount of bleeding and some pain at the biopsy site are the most common side effects from a biopsy of the adrenal gland. Rarely, an infection may occur following a biopsy.

Surgery

The side effects from the surgery are the same as you would have if you received standard surgery for an adrenal tumor at a major medical center. There should be no additional side effects from taking the additional tissue during the operation.

Radiation from the biopsy

This research study involves exposure to radiation from the biopsy of your adrenal tumor. Please note that this radiation exposure is **not** necessary for your medical care and is for research purposes only. The total amount of radiation you will receive in this study is from one CT scan of your adrenal glands. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving minimal risk and necessary to obtain the research information desired.

Tumor biopsy will be done by a specialist using the CT scanner or ultrasound to guide the biopsy needle into the tumor to ensure accuracy. To collect the research biopsy, you will be exposed to

one CT scan. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this procedure is 0.80 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet,. *An Introduction to Radiation for NIH Research Subjects.*

Potential Benefits of Participation

Are there benefits to taking part in this study?

Data from this study may also be useful in developing new ways of diagnosing adrenal tumors but you may not benefit directly from this.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- Getting treatment or care for your adrenal tumor without being in a study
- Taking part in another study

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs even if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Stopping Study Participation

Your doctor may decide to take you off the study if he/she believes that it is in your best interest.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the Center for Cancer Research, NCI or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These data will be stripped of identifiers such as name, address or account number, so that they may be used

for future research on any topic and shared broadly for research purposes. Your data will be used for research purposes only and will not benefit you. It is also possible that the stored data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored data used for future research, please contact us in writing and let us know that you do not want us to use your data. Then your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Electron Kebebew M.D., Building 10, Room 4-5952, Telephone: 240-760-6153 or Roxanne Merkel, R.N., Telephone 240-760-6058. You may also call the Clinical Center Patient Representative at (301) 496-2626.If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM AUGUST 8, 2016 THROUGH AUGUST 7, 2017.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____